**DRAFT DISCUSSION POINTS FOR SCREENING AND TESTING DONORS OF HUMAN TISSUE INTENDED FOR TRANSPLANTATION AND HUMAN REPRODUCTIVE TISSUE, AND FOR ESTABLISHMENT REGISTRATION.**

Intended for discussion at the FDA
Workshop on Human Tissue Intended for Transplantation
and Human Reproductive Tissue: Donor Screening and Infectious Disease Testing

(to be held 1:00 to 5:30 on 3/24/95)

## I. INTRODUCTION

This document is intended as an outline for discussion of issues related to the recovery, processing, storage, or distribution of human tissue intended for transplantation and human reproductive tissue intended for insemination of a person other than the donor's spouse or sexual partner or implantation into a recipient other than the oocyte donor.

The Interim Rule was issued because of an immediate need to protect the public health from the transmission of HIV infection and hepatitis infection through transplantation of tissue from donors infected with or at risk of these diseases. Additionally, recommendations from the CDC favor the screening of semen donors for sexually transmitted diseases (STDs). Reports of transmission of HIV, hepatitis, and other STDs support the need for such screening as well as testing for the infectious agents or antibodies to these diseases. Also the possibility of transmission of infectious agents with donor oocytes or banked human embryos, which puts both the recipient and fetus at risk, support the need for screening and testing of other reproductive tissues as well as semen.

## II. PROCEDURES

### A. Donor Testing for Human Tissue intended for transplantation

1. FDA believes that donor infectious disease marker testing criteria as previously stated in the Interim Rule should be used in the donor screening process for human tissue. All human tissue intended for transplantation must be from donors whose blood tests negative for hepatitis B surface antigen, antibodies to the hepatitis

C virus, and antibodies to the human immunodeficiency virus Type 1 and Type 2.

2. The testing shall be done by laboratories appropriately certified for those tests performed and in good standing under the Clinical Laboratories Improvement Amendments (CLIA) of 1988. The tests used shall be approved for such uses by FDA. The tissue shall be accompanied by records to indicate that the testing was done and that the samples were found to be negative for anti-HIV-1, anti-HIV-2, HBsAg, and anti-HCV using an FDA approved screening test. For samples of cadaveric blood, screening tests which have been approved for testing cadaveric blood must be used, when available.

3. Tissue must be quarantined from:

a. a donor whose blood specimen has tested repeatedly reactive on a screening test for anti-HIV-1, anti-HIV-2, HBsAg, or anti-HCV,

b. adult donors who, within 48 hours prior to taking the blood sample, have been transfused with more than four units of whole blood,

c. adult donors who were infused with a volume of colloid or crystalloid sufficient to result in a plasma dilution of 50% or greater at the time of sampling, or

d. children under 12 years of age who have received any infusion of a colloid or crystalloid or transfusions of blood or blood components within 48 hours of blood sampling.

Quarantine means the identification of human tissue as not suitable for use or that has not yet been characterized as being suitable for human use, and includes the storage in an area clearly identified for controlled sequestration. Tissue is considered not suitable for transplantation if from donors that have not been tested for HIV, HBV, or HCV, regardless of the reason that testing was not be done. Quarantining due to transfusion is not necessary if a pre-transfusion blood sample was available for testing or if an adequate algorithm was employed to ensure that there was not plasma dilution sufficient to alter the test results.

## B. Donor screening for tissue intended for transplantation

1. The FDA believes that donor screening for high risk behavior for exposure to HIV and hepatitis viruses should be accomplished through a next of kin interview and review of the donor's medical history as well as review of autopsy reports and medical records. A "next of kin" is considered to be an individual who is aware of the donor's medical history and social behavior; such as the nearest available relative of the donor, a member of the donor's household, or other individual with an affinity relationship to the donor. For corneas retrieved under authorization of a specific state or territorial medical examiner law, the relevant medical history shall include all available medical, coroner and autopsy records, and an interview with the next of kin when possible.

2. Tissue should not be accepted from donors who met any of the following:

a. men who have had sex with another man within the preceding 5 years[1],

b. persons who have injected drugs for a non-medical reason in the preceding 5 years, including intravenous, intramuscular, and subcutaneous injections of recreational or illegal drugs[1],

c. persons with hemophilia or related clotting disorder who have received human-derived clotting factor concentrates[1],

d. persons who have had sex in exchange for money or drugs in the preceding 5 years[1],

e. persons who have had sex in the preceding 12 months with any person described in the 4 items above or with any person suspected of having HIV, HBV or HCV infection[1,8],

f. persons who have been exposed within the last 12 months to known or suspected HIV, HBV, and/or HCV infected blood through percutaneous inoculation (needlestick) or through contact with an open wound, non-intact skin, or mucous membrane[1,7,10],

g. children meeting any of the exclusionary criteria for adults[1],

h. children 18 months of age or less born to mothers who are HIV-infected or at risk for HIV infection and who have been breast fed within the preceding 12 months, regardless of HIV status[1],

NOTE: Children over 18 months of age who are born to mothers infected with HIV or at risk for infection, who have not been breast fed within the preceding 12 months, and whose HIV antibody test, physical examination, and review of medical records do not indicate evidence of HIV infection can be accepted as donors[1].

i. current inmates of correctional systems (including jails and prisons) and individuals who have been incarcerated for more than 72 consecutive hours during the previous 12 months[1],

j. close contact with another person having viral hepatitis within one year preceding donation[8],

k. persons who have been victims of rape during the preceding 12 months[7],

l. persons who have had or have been treated for syphilis or gonorrhea during the preceding 12 months[7,10], or

m. persons who within one year of donation have undergone acupuncture, ear and/or body piercing or tattooing in which sterile procedures were not used, or where it is unknown if sterile procedures were used[8].

FDA believes that direct questions addressing the above criteria should be asked in the next of kin interview to determine if these events occurred. If these risk factors are reported within the time period specified in any available information, the tissue should not be used.

3. In addition to the requirements that a donor should test negative for HIV, HBV, HCV and be screened and found to have none of the indicated behavioral risk factors, a donor should also be free from clinical signs or symptoms

of HIV and hepatitis. Based on the donor's medical history (including next of kin interview), physical examination, medical records, autopsy report and laboratory test results, tissue donors should be free from evidence of:

a. HIV infection or high risk of exposure to HIV such as a diagnosis of AIDS or HIV infection, unexplained weight loss, night sweats, blue or purple spots on the skin or mucous membranes typical of Kaposi's Sarcoma, unexplained lymphadenopathy of longer than one month, unexplained temperature of over 100.5°F (38.6°C) for more than 10 days, unexplained persistent cough or shortness of breath, opportunistic infections, unexplained persistent diarrhea, a history of male to male sexual contacts, a history of sexually transmitted diseases, needle tracks or other signs of parenteral drug use[1,7], or

b. a diagnosis of hepatitis B or C infection, which would include physical evidence of clinical hepatitis such as yellow jaundice or hepatosplenomegaly (records of laboratory data such as ALT, AST, bilirubin or prothrombin time may assist in making a donor suitability determination)[5].

**C. Donor Testing for Reproductive Tissue**

1. Testing of reproductive tissue donors should include all tests recommended for human tissue for transplantation. FDA also believes that donors of human reproductive tissue should be tested for physical evidence of, and/or exposure to, communicable diseases that can be transmitted through artificial insemination, fertilization and/or implantation. Tests should include the following: a complete blood count, urinalysis, urine culture, antibodies to HIV-1, antibodies to HIV-2, hepatitis B surface antigen, antibodies to hepatitis C virus, antibodies to human T-cell lymphotropic virus type I, antibodies to CMV, serological test for syphilis, semen white blood cell count, urethral or cervical swab for Chlamydia trachomatis, Neisseria gonorrhoea, Mycoplasma hominis, and Ureaplasma urealyticum.

2. All testing should be performed by a laboratory certified to perform such tests under the Clinical

Laboratories Improvement Amendments (CLIA) of 1988 according to FDA approved directions for use. When available, only FDA cleared or licensed serological marker tests should be used.

3. FDA is evaluating donor testing requirements for release from quarantine for semen. FDA is considering a provision that would require, at the time of donation of semen, that the donor be tested for HIV, HBV, HCV, and all other tests listed in Section IIC1. Semen would only be accepted if the donor is negative for all tests and screening. Such donated semen would then be placed in quarantine for six months in an appropriate method of storage. After six months, the donor would be retested for communicable disease serological markers to establish that results are negative. If serological marker test results were negative, the donated semen would be released from quarantine.

**D. Donor Screening for Reproductive Tissue**

1. FDA believes that screening of reproductive tissue donors should include the taking of a medical history to assure freedom from sexually transmitted diseases (STD), genitourinary diseases, and freedom from risk factors for HIV, hepatitis B, and hepatitis C infection. FDA is considering whether donor screening criteria for high risk behavior for exposure to HIV and hepatitis viruses should be adapted for use in screening reproductive tissue donors. FDA believes that reproductive tissue should not be accepted from donors meeting any of the criteria as listed in Section IIB2 and 3 of this outline.

2. FDA also believes that tissue should not be accepted from donors with a history of having received within one year preceding donation, human blood, blood components or any derivative of human blood (except in the case of specific immunization of Source Plasma donors (21CFR 640.66)).[8]

3. Screening should also include a physical examination to establish that the donor is in good general health and is free from any signs and symptoms of bloodborne infections, systemic communicable diseases, STDs, genitourinary communicable diseases, and any signs and/or symptoms of illegal injectable drug use.

4. FDA believes that repeat donors must have a complete donor suitability determination performed every 60 days. For those who donate less frequently than every 60 days, a complete donor suitability determination should be performed with every donation. For repeat donors where less than 30 days have elapsed, an abbreviated donor suitability determination may be performed. An abbreviated donor suitability determination should consist of all tests indicated in section IIC1, a review and update of the donor medical history obtained at the last donation, and an abbreviated physical examination.

## III. DISCUSSION OF POSSIBLE REGISTRATION OF TISSUE ESTABLISHMENTS

FDA is considering requiring tissue establishments to register with FDA. Such registration would allow FDA among other things, to transmit information concerning updated recommendations, as well as, recall alerts to all establishments.

If codified, such a requirement would necessitate annual registration of any establishment or entity engaged in the recovery, processing, storage, or distribution of human tissue for transplantation or human reproductive tissue. As a part of such a process, the registrant would be required to provide the agency with:

1. basic identifying information including the name, address, telephone number, and fax number for the establishment, the name of the reporting individual, and information on the type of ownership of the facility such as non-profit, partnership or government,

2. basic types of tissue handled by the registrant such as musculo-skeletal, ocular, or reproductive. The methods of donor screening and the infectious disease testing used for each type of tissue handled,

3. information concerning the type of manufacturing service such as collection/recovery, processing, donor testing, product testing, storage,or distribution. The location of such service and type of tissue handled on-site or if off-site, the name and address of the contracted organization that provides the service, and

4. information concerning voluntary certification of the establishment.

## IV. REFERENCES


1. PHS Guideline for Preventing Transmission of HIV through Transplantation of Human Tissue and Organs, MMWR 1994:43, 1-17.

2. PHS Guideline for Screening Donors of Blood, Plasma, Organs, Tissues and Semen for Evidence of Hepatitis B and Hepatitis C, MMWR 1991:40, 1-17.

3. PHS Guideline for Semen banking, organ and tissue transplantation, and HIV antibody testing. MMWR 1988:37,, 57-8,63.

4. FDA Interim Rule for Human Tissue Intended for Transplantation, December 14, 1993, Federal Register, Vol 58, No. 238, p 65514.

5. FDA Recommendations to Blood Establishments, for "Donor Suitability Related to Laboratory Testing for Viral Hepatitis and a History of Viral Hepatitis, 12/22/93.

6. FDA Revised Recommendations to Blood Establishments for "Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)", 8/5/93

7. FDA Revised Recommendation for "The Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products", 4/23/92

8. FDA Revised Recommendations to Blood Establishments for "Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)", 4/23/92.

9. FDA Recommendations to Blood Establishments "Concerning Testing for Antibody to Hepatitis B Core Antigen (Anti-HBc)", 9/10/91.

10. FDA Revised Recommendations to Blood Establishments, "Revision to 26 October 1989 Guideline for Collection of Blood or Blood Products from Donors with Positive Tests for Infectious Disease Markers (High Risk Donors)", 4/17/91.

11. FDA Recommendation to Blood Establishments for "HTLV-I Antibody Testing", 11/29/88 and 7/6/89.